REVIEW ARTICLE

The Significance of Adaptive Design in R&D in Japan

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In the past decade, the number of drug and biological product submissions to the United States Food and Drug Administration has been slowly declining, while biomedical research spending has increased. A similar situation can also be seen in Japan: the number of domestic clinical trials is diminishing, and the cost of conducting a trial is rising. To prevent further decreases in the number of clinical trials, there is a need for an innovative strategy such as an adaptive design in research and development. Integrative celerity research aims to combine critical path and translational research, and seek update and participation in global clinical research. Participation in global studies through an adaptive design raises statistical concerns, which can be dealt with by adapting bridging studies. As a result of the restricted number of patients before approval in the adaptive design, safety issues must be guaranteed. Thus, establishing an effective and strong safety network between medical facilities is crucial. Japan's mission is to develop better drugs more efficiently and to investigate new drug methodologies for participation in global/Asian studies. Team work between clinical trial specialists, computer scientists, medical doctors, and statisticians is important for the success of both adaptive design and construction of a safety network between medical facilities in Japanese research and development. [*J Formos Med Assoc* 2008;107(12 Suppl):S9–S13]

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In the past decade, the number of drug and biological product submissions to the United States Food and Drug Administration (FDA) has been slowly declining, while biomedical research spending has increased. Investment in the discovery phase per successful drug was the same between 1995–2000 and 2000–2002. On the other hand, investment in critical path initiatives almost doubled in 2000–2002 compared with 1995–2000. The increased focus on biomedical research allows for possible discovery of innovative products that may provide prevention, treatment and cure of serious diseases that affect contemporary society. Scientific knowledge is advancing, yet using this knowledge to help society is at a standstill. Increased biomedical spending, combined with fewer drug submissions, leads to critical paths becoming very expensive and the cost of success of a compound is greatly escalated.

Possible reasons and explanations for this phenomenon of decreased success are that the tools and concepts of the last century are being used to evaluate this century's drug candidates. This indicates that recently discovered innovative drugs are still evaluated by ordinary endpoints, which cannot measure the proper profile of the innovative drugs. In a 2004 FDA and industry workshop, Dr Janet Woodcock noted that "currently, one out of every two phase III trials fails", which means that the success rate of clinical trials is

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decreasing to < 50% in the United States. To combat this decrease, FDA's Critical Path Initiative (CPI) believes that it is necessary to "develop new, publicly available scientific and technical tools—including assays, standards, computer modeling techniques, biomarkers, and clinical trial endpoints—that make the development process itself more efficient and effective and more likely to result in safe products that benefit patients".[1] Therefore, a new approach to develop and evaluate the efficiency and effectiveness of promising innovative drug candidates is required.

A similar situation can be seen in Japan: the number of domestic clinical trials is diminishing, and the cost of conducting a trial is rising. For example, in 1992, only 18.3% of compounds were first developed outside of Japan by Japanese domestic companies, but in 2000, 43.2% of the compounds were developed outside of Japan. It is also known that the speed of conducting clinical trials in Japan is very slow. The three factors of high cost, slow speed, and foreign conduct of clinical trials by Japanese domestic companies comprises the phenomenon called "hollowing out of clinical trials" in Japan. To prevent further decrease in the number of clinical trials in Japan, we need a new approach to clinical research. A possible solution is an adaptive design in research and development, which borrows accumulated clinical information, thus modifying the trial design in terms of required sample size and/or dropping one or two arms of a phase III trial, for confirmation of the efficacy/safety of the treatment being tested.

Concept of Integrative Celerity Research in Japan

Integrative celerity research (ICR), proposed by Imura, aims to combine both critical path research and translational research.[2] Figure 1 shows the concept of ICR. In Japan, translational research activity has been growing, and the results of the research have been published in leading journals such as *Science*. Unfortunately, clinical research activity in Japan has not increased and is not recognized when compared with translational research. Therefore, the purpose of ICR is to unite the achievements of basic science with the activity of clinical research. Not only does ICR aim to combine critical and translational research, new perspectives on clinical research can be formulated by the introduction of bridging studies and the participation of Japan in Asian and global studies. In 1998, the E5 guideline, which allows extrapolation of the results of foreign clinical trials to Japan for the approval of new drugs, was adopted. More than 40 compounds have been approved through

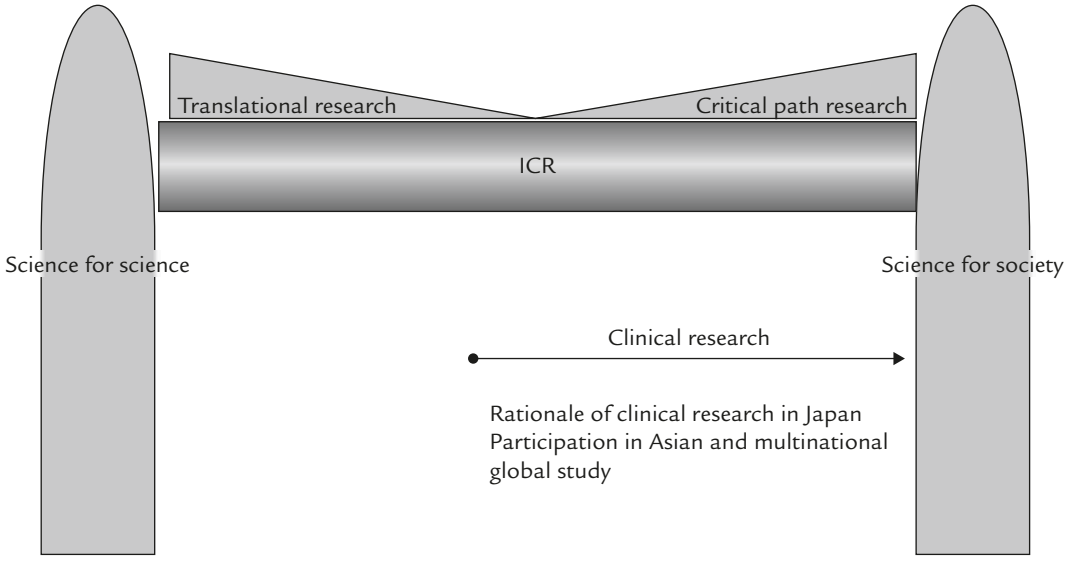

Figure 1. Concept of integrative celerity research in Japan.

extrapolation of foreign clinical trial results by conducting a small study, known as a bridging study.[3,4] Bridging studies provide the necessary information regarding differences in ethnic, intrinsic and extrinsic factors among foreign and Japanese subjects. We can apply the concept of bridging studies to simultaneous ongoing global studies with further extensive experience. The key factor in both bridging and global studies is to recognize an appropriate dosage in Japanese patients.

Adaptive Design in Japan

Currently, adaptive design in the US and EU combine phase II and III with a single assessment in each phase. In order for Japan to participate in global studies, Japan will also have to apply the concept of adaptive design to combine phase II and III. Since dosage determination is a key, adaptive design must be modified. The modified adaptive design is much more complex than the designs used in the US and EU. Figure 2 summarizes the main idea of adaptive design in Japan. In phase II trials, a new dosage such as a low-low dosage may be introduced to investigate intrinsic factors in Japanese patients. As part of translational research in Japanese trials, a futility assessment using surrogate/biomarkers, computer modeling and pharmacogenomics is needed as a primary assessment in phase II trials to determine the dose–response curve. Thus, in the Japanese design, two assessments in phase II will be required. The second assessment of phase II will investigate the probability of success by modeling, validation of surrogate/biomarkers, and patient variability through pharmacogenomic information.

This approach raises statistical concerns and issues. The small sample size in Japanese trials compared with that in other countries raises the concern of evaluating efficacy and producing adequate power in the trial. To combat this concern, the concept in bridging studies of applying similarity of efficacy among countries in the same clinical trial may be used. Determination of an appropriate dosage range for the Japanese population is another issue that has to be addressed. An additional dosage must be introduced as must the application of the concept of similarity to determine whether or not the new dosage is appropriate for a Japanese population. To implement the suggested adaptive design in Japan, there is a need for the accumulation of clinical data such as efficacy and dosage through an electronic data capture (EDC) system. Currently, there are two types of good clinical practice (GCP) in Japan, J-GCP and ICH-GCP.[5,6] The different GCPs prevent implementing an EDC system in Japan. To conduct and evaluate the clinical data results in a timely fashion, professional clinical specialists in regulatory agencies, academia and industry are needed. Training these professionals demands adequate

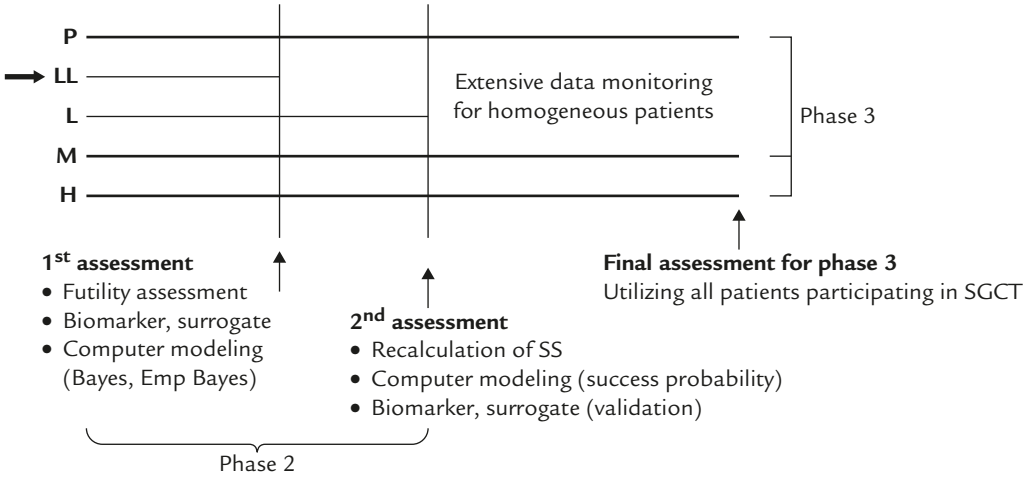

Figure 2. Application of possible approach.

educational programs, not only for biostatisticians, but also for clinicians.

Construction of a Safety Network System

Application of this new approach causes major concerns regarding safety, because the number of exposed patients will decrease through possible extrapolation of foreign clinical data for evaluation of efficacy. A large database to detect severe and regionally oriented adverse events will be required. A possible solution is to build a strong safety network between hospitals to construct and evaluate the data from all patients who are prescribed the drug after approval. The Ministry of Health, Labor and Welfare has established a research grant to focus on implementing a network between hospitals. This system aims to develop a strong and validated EDC system to collect clinical data, monitor patients, and detect unexpected adverse events, as well as building a database of patient background details for signal detection and pharmacoepidemiology.

Overall, there are two main steps in creating an efficient and safe networking system in Japan. Figure 3 shows the construction of a network system in Japan. A safety data capturing system within a medical facility must be developed. Within each medical facility, unification of patient medical records regarding patient background, dosage, efficacy and safety of the patients is essential. In most cases, medical records exist in several different departments of the medical facility. Data about each patient must be unified within each medical facility, followed by the unification of the databases from all the medical facilities into one main data center. Compiling patient data into one center allows for a simultaneous monitoring system, which will help to detect unexpected adverse events and analyze safety profiles according to actual drug dosage and duration of treatment.

Similar to the FDA's CPI, Japan's mission is to develop better drugs more efficiently, with new drug development methodologies, by participating

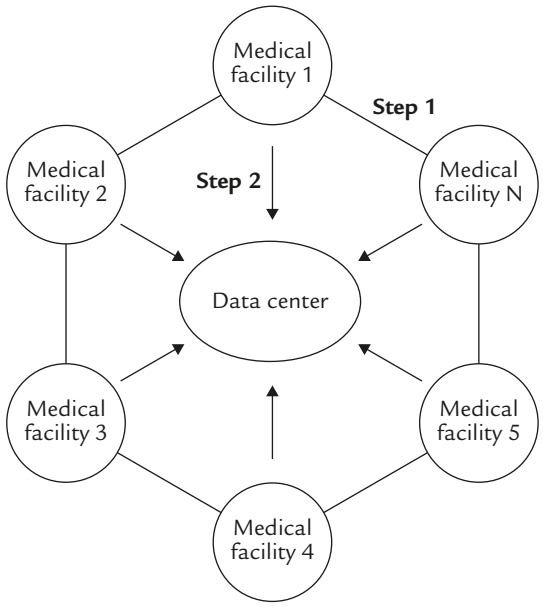

Figure 3. Construction of a safety network system in Japan.

mainly in global/Asian studies. Although developing better drugs in a time-efficient manner is important, patient safety must be a priority. The importance of pharmacovigilance by monitoring patients, developing a patient database through a safety network, and a unified EDC system between Japan and other Asian countries are all factors that will help maintain patient safety. Finally, team work between clinical trial specialists, computer scientists, medical doctors, and statisticians is important for the success of adaptive design in Japanese research and development.

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